

(9)



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

**0 277 383
A1**

(2)

EUROPEAN PATENT APPLICATION

(21) Application number: 87202593.7

(51) Int. Cl. 4: **A61K 7/28**

(22) Date of filing: 21.12.87

(30) Priority: 08.01.87 NL 8700025

(43) Date of publication of application:
10.08.88 Bulletin 88/32

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(71) Applicant: **Douwe Egberts Koninklijke
Tabaksfabriek- Koffiebranderijen-Theehandel
N.V.
Keulsekade 143
NL-3532 AA Utrecht(NL)**

(72) Inventor: **Hoogendoorn, Hendrik
Zilver Schoon 2
NL-2923 GP Krimpen a/d IJssel(NL)**

(74) Representative: **Smulders, Theodorus A.H.J.
et al
Vereenigde Octrooibureaux Nieuwe Parklaan
107
NL-2587 BP 's-Gravenhage(NL)**

(54) **Mouth care products.**

(57) Mouth-care products containing an oxidoreductase and a combination of an 8-hydroxy-quinoline and a compound yielding zinc ions.

EP 0 277 383 A1

Mouth care products

The invention relates to tooth-cleaning agents containing oxidoreductase, and to methods for the preparation thereof.

The Dutch Patent Specification 150,332 describes tooth-cleaning agents which, in addition to the ingredients which are usual for said agents, also contain an enzyme which yields hydrogen peroxide on breaking down a substrate. Depending on the nature of such an oxidoreductase, the relevant substrate and/or another enzyme which can convert compounds present in the mouth or on the tooth surface into a substrate for the oxidoreductase used are also added to the tooth cleaning agent.

Use is made of such an enzyme system yielding hydrogen peroxide to achieve normalization of the mouth flora via the lactoperoxidase (saliva peroxidase) present in the saliva and the hypothiocyanite additionally formed, as a result of which the formation of harmful acids is prevented.

According to this principle, the acid-forming bacteria are not killed but a temporary inactivation takes place of the enzymes which occur in said bacteria and which are responsible for the acid formation.

It has been found, however, that under certain circumstances said inactivation does not take place, or takes place to a reduced extent, which depends, inter alia, on the nature of the food and the frequency at which it is consumed.

A large number of articles have previously proposed adding bactericidal substances to tooth-cleaning agents in order to kill the acid-forming bacteria. The great disadvantage thereof is that this may lead to the production of resistant strains and the growth of undesirable micro-organisms.

If bacteria are killed but not removed, autolysis of the dead cells will also occur as a result of which the surviving cells have additional nutrient substances at their disposal which is the very thing which promotes harmful acid formation.

Surprisingly, it has now been found that the use of a combination of zinc ions and an 8-hydroxyquinoline in concentrations in which each of the two components separately and also in combination have no bactericidal action increases the inactivation of the acid-forming bacteria in an oxidoreductase-containing tooth-cleaning agent, even under the unfavourable conditions outlined above.

The invention therefore relates to oxidoreductase-containing tooth-cleaning agents, optionally containing a substrate for such an oxidoreductase and/or an enzyme which can yield said substrate, by adding thereto a combination of an 8-hydroxyquinoline and a compound yielding zinc ions, and to methods for the preparation thereof.

As stated, the combination of zinc ions and an 8-hydroxyquinoline is used in such concentrations that neither the components separately nor the combination has a bactericidal action.

The 8-hydroxyquinoline concerned is used in a concentration which is between $5 \cdot 10^{-5}$ and 10^{-1} % by weight of the tooth-cleaning agent, and zinc (in ionic form) in a concentration which is between 10^{-5} and 10^{-1} % by weight.

It has been found that the use of the 8-hydroxyquinoline concerned in a concentration of 5×10^{-4} to 10^{-3} % by weight and of zinc (ions) in a concentration of 10^{-4} to 5×10^{-3} has an especially effective action.

The zinc compound to be used may be any pharmaceutically acceptable, water-soluble zinc compound derived from inorganic or organic acids such as zinc sulphate, zinc citrate, zinc gluconate, zinc acetate etc., but usually the zinc salt of the 8-hydroxyquinoline is used.

The 8-hydroxyquinoline to be added may be 8-hydroxyquinoline itself, or derivatives thereof, such as substituted derivatives, esters, for example the acetate or sulphate, or acid addition salts thereof.

Of the substituted derivatives, consideration is preferably given to the halogenated derivatives, such as the 5-halo, 7-halo, and 5,7-dihalo derivatives.

The combination of zinc ions and an 8-hydroxyquinoline described above is added to an oxidoreductase-containing tooth-cleaning agent.

Said oxidoreductase may be any oxidoreductase yielding hydrogen peroxide, such as lactate oxidase, glucose oxidase, pyruvate oxidase, xanthine oxidase etc.

The quantity of oxidoreductase is usually between 0.01 and 500 units per gram/millilitre of the tooth-cleaning agent.

A unit of enzyme is understood to mean the quantity which breaks down 1 μ mol of substrate per minute at 30 °C and under standard conditions.

One or more other enzymes, preferably hydrolases, such as carbohydrases and proteases, can also be added in addition.

Preferably glucose oxidase is used as oxidoreductase, optionally in the presence of amyloglucosidase

as hydrolase, and/or glucose as substrate.

The effect of the combination according to the invention was manifestly demonstrated by means of human saliva, the mouth flora of which has been stimulated, i.e. has acquired an increased resistance to inactivation, by treatment with glutathion.

5 Said saliva was introduced into a number of small containers, 1% of fructose being added, and the acid formation was measured by titration at a certain pH and temperature after adding a substance to be determined.

10 From the table below it is then evident that adding one of the components comprising zinc, 8-hydroxyquinoline and glucose oxidase, and combinations of two of the said components does not slow down the acid formation, while the total combination does in fact do this.

Table

15	1. $\text{ZnSO}_4 \cdot 7 \text{H}_2\text{O}$	10^{-3} % by weight	acid formation
	2. 8-hydroxyquinoline	10^{-3} % by weight	acid formation
20	3. $\text{ZnSO}_4 \cdot 7 \text{H}_2\text{O}$ + 8-hydroxyquinoline combination of 1 and 2		acid formation
25	4. Glucose oxidase (see Dutch Patent Specification 150,332)		acid formation
30	5. Combination of 1 + 4		acid formation
	6. Combination of 2 + 4		acid formation
35	7. Combination 3 + 4		no acid formation

40 The tooth-cleaning agents according to the invention can be converted to various forms, such as to the form of a toothpaste, mouthwash, tablet, chewing gum or other conventional form.

In addition to the components according to the invention, said tooth-cleaning agents may also contain the other usual excipients, such as abrading and polishing agents, thickening agents, colourants, sweetening agents, fluorine compounds, and the like.

45 The invention is explained in more detail by reference to the following compositions, without, of course, being restricted thereto.

Example 1

50	Toothpaste	Sorbitol	22% (by weight)
	Silica		22%
	Ethoxylated fatty alcohol		3%
	Carragheen		1.5%
	Sodium benzoate		0.1%
55	Flavouring		0.6%
	Sodium saccharinate		0.1%
	Amyloglucosidase		18 U/g
	Glucose oxidase		6 U/g

Zinc sulphate 7 H₂O 10³ %
 8-hydroxyquinoline 10³ %
 Water to 100%

5

Example 2

Toothpaste Glycerol 15% (by weight)
 Aluminium oxide hydrate 35%
 10 Ethoxylated fatty alcohol 2.5%
 Carrageen 2%
 P.H.B. esters 0.15%
 Flavouring 1.2%
 Sodium fluoride 0.24%
 15 Mutanase 15 U/g
 Glucose oxidase 8 U/g
 Invertase 5 U/g
 Zinc gluconate 8×10^4 %
 5-chloro-8-hydroxyquinoline 10³ %
 20 Water to 100%

Example 3

25 Mouthwash Glycerol 15% (by weight)
 Xylitol 15%
 Flavouring 0.05%
 Tween 80 2%
 Propyl p-hydroxybenzoate 0.1%
 30 Potassium thiocyanate 0.02%
 Sodium citrate 0.2%
 Amyloglucosidase 4 U/g
 Glucose oxidase 1 U/g
 Zinc citrate 2×10^4 %
 35 8-hydroxyquinoline sulphate 10^4 %
 Water to 100%

Example 4

40 Lozenge Sorbitol 1500 mg
 Encapsulated flavouring 10
 Sodium stearate 10
 Phosphate buffer pH = 7 50
 45 P.V.P. 20
 Zinc 8-hydroxyquinolate 0.16 mg
 Glucose oxidase 50 U
 Amyloglucosidase 100 U

50

Example 5

Effervescent tablet NaHCO₃ 40mg
 Citric acid 20
 55 P.V.P. 2
 Sorbitol 24
 Encapsulated flavouring 2
 Glucose 2

Glucose oxidase 10 U
Lactoperoxidase 100 U
Potassium thiocyanate 1
Zinc 8-hydroxyquinolate 0.3 mg
5 Dissolve in: 15 ml of water.

Claims

10

1. Method for the preparation of oxidoreductase-containing mouthcare products, characterized in that, in addition to an oxidoreductase yielding hydrogen peroxide, an 8-hydroxyquinoline and a compound yielding Zn ions is added.
- 15 2. Method according to claim 1, characterized in that 8-hydroxyquinoline, or a derivative of 8-hydroxyquinoline substituted by one or more halogens, is used.
3. Method according to claim 1 or 2, characterized in that a zinc salt of an 8-hydroxyquinoline is used.
4. Method according to one or more of the preceding claims, characterized in that the 8-hydroxyquinoline concerned is used in a concentration which is between $5 \cdot 10^{-5}$ and 10^{-1} % by weight, and zinc
20 (in ionic form) in a concentration which is between 10^{-5} and 10^{-1} % by weight.
5. Mouth care products according to one of the claims 1 to 4 incl.

25

30

35

40

45

50

55



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 87 20 2593

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	CHEMICAL ABSTRACTS, vol. 72, no. 20, 18th May 1970, page 232, abstract no. 103745n, Columbus, Ohio, US; & JP-A-70 02 752 (EISAI CO., LTD.) 29-01-1970 * Abstract *	1,2,5	A 61 K 7/28
A	US-A-4 082 841 (M. PADER) * Claims *	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			A 61 K 7/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 25-03-1988	Examiner WILLEKENS G.E.J.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	